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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/742,520	12/20/2000	Ilham Saleh Abuljadayel	674528-2001.2	9656

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
742,520	ABULJADAYEL
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 5/21/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 47-72 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 47-72 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/21/03 has been entered.

After entry of this amendment claims 47-72 are active. Also, the IDS filed 5/21/03, the IDS of 12/23/03 and the declaration filed 12/23/03 have been entered for consideration.

Applicant's change of title and submission of a new abstract with the amendment of 5/21/03 are acknowledged.

The amendment filed 5/21/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: deletion of material in the paragraph starting at page 34, line 12 is new matter, since this changes the concept of what is meant by "CD45 low" and hence is as much new matter as any addition.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 57-59 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The HLA-DR

receptor of claim 56 inherently has a beta chain with homologous regions. Therefore claims 57-59 fail to further limit claim 56.

Applicant has merely traversed on the basis that claims with similar dependencies were allowed in Pat. 6,090,625. The examiner notes that he is not obligated to allow claims merely because similar claims were allowed in a previous application. In re Haller 73 USPQ 403; Ex parte Gwinn 112 USPQ 439. Applicant has not argued by addressing the pertinent fact in question --whether or not HLA-DR does or does not inherently have a beta-chain.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Regarding 112, second paragraph rejections of record, that of claim 54 has been withdrawn due to the amendment.

Claims 47-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low" in claim 47 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant's original disclosure has admitted (page 34, lines 5-6) that the classification of cells as "CD45 low" is arbitrary. Since this classification is "arbitrary" the metes and bounds of the claimed invention are unclear.

Applicant urges that the claim is now definite because of the amendment to the specification deleting the teaching that the term "CD45 low" is arbitrary. This deletion does not since the examiner considers the deletion to the new matter (objection under 35 USC 132 supra), and not the deletion of any obvious error. In any event, even if the deletion is not new matter, the examiner considers what was deleted to represent the state of mind of what applicant considered her invention at filing.

Applicant has also referred to various journal articles that use terms "low" and "high" or symbols such as "+" or "+++" to designate antigen density. While these terms may be in common usage, they are qualitative and subjective; there is no clear indication that what one investigator grades as "+" used not be graded by another as something else--e.g. "+/-" if considered lower than "low" or "++" if considered on bit higher than "low." The term "low" thus remains indefinite for purposes of meeting requirements of patentability.

Regarding the 112, first paragraph, new matter rejections of record, the examiner notes the following rejections are withdrawn:

The rejection of claim 49 for reciting "2 to 24 hours" is withdrawn. This is considered consistent with In re Wertheim 191 USPQ 90 with respect to ranges disclosed.

The rejection of claim 52 for reciting "bone marrow" is withdrawn, due to the amendment.

The 112, first paragraph, new matter rejections of record that are maintained are the following:

Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 53 contains new matter because thus is no teaching that the population of CD45 low cells express MHC class I or class II.

The vague generalization that set forth at specification page 2, lines 28-29 that "most" undifferentiated or differentiated cells express MHC class I and /or II antigens" fails to imply anything about the nature of the CD45 low cells at issue. This generalization does not permit one to conclude that CD45 low cells express none of class I and II; it does not permit one to conclude that CD45 cells express both class I and II; it does not permit one to conclude that only one of class I and II are expressed (and, if so, which one). In the absence of being able to draw any conclusions therefrom, the statement at page 2, lines 28-29 is insufficient to support what applicant claims. Given this argument, examiner will not further consider applicant's logic at page 8.

Claims 67-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. Claims 67-72 contain new matter because applicant's exemplification of CD45 low cells has not shown that any of these cells have the recited properties of differentiation.

Applicant's response is that one can properly extrapolate the properties recited in claims 67-72 from CD34+ to CD45 low cells because CD34+ cells are CD45 low. This statement is illogical because applicant's claims do not recite that the cells are both CD34+ and CD45 low. It is also possible for there to be CD45 low cells which have no CD34+ and thus would not be expected to have the multipotential differentiating capabilities of CD34+ cells.

The following 112, first paragraph, lack of possession rejections are maintained.

Claims 47-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of the genus of agents that "operably engage" committed cells such that the relative number of CD45 low cells increases (as required in claim 47).

Claims 63-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of the genus

of biological response modifiers (claim 63) to be used in conjunction with the agent (of claim 47).

The descriptions of the "agent" and "modifier" as set forth in the claims and in the disclosure are merely functional--i.e. expressions of a desired result. This does nothing to describe what the agents and the modifiers are as a genus.

Applicant has urged that claims 1 and 18 of Pat. 6,090,625 recite the generic language. This is not convincing that the rejection should be withdrawn, as each case is to be decided on its own merits. Ex parte Gwinn 112 USPQ 439.

Applicant has urged that guidance is provided in the specification as to what agents may be used. The examiner has noted, in the office actions of 3/6/02 and 11/21/02, that what guidance is given points to a few species which are not representative of the genus.

Applicant has urged her invention is pioneering and that she teaches one how to screen for others. The examiner considers that precisely because applicant's invention is unusual, and pertains to a field that has no conventional knowledge, she should be limited to what she specifically described. If applicant were reciting a conventional genus of agents, such as pharmaceutically acceptable diluents for a drug, then one would have been able to envision the genus; in a pioneering field one cannot have such envisioning knowledge. Applicant's additional argument that she has taught screening methods might be applicable to enablement but it is not for description. Vas Cath v. Mahurkar 19 USPQ 2d 1111.

Applicant has again urged that the declaration of 9/6/02 executed by Dr Abuljadayel has shown additional agents, beyond those exemplified in the specification. As previously noted by the examiner (11/21/02) what was found post filing does not demonstrate possession at the filing date. Also, even if the additional species shown in the 1.132 declaration were in the specification, the exemplified species would be of such diverse nature that the genus would not be described. The declaration further, has failed to show how to specification particularly pointed to the agents which were later discovered as of 9/6/02.

Rejections under 35 USC 112, first paragraph with respect to enablement are maintained infra.

Claims 47-61 and 63-72are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of agents which are antibodies directed to the alpha or beta chan of MHC class I or II receptors, does not reasonably provide enablement for the use of any agent that operably engages committed cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to pracitce the invention commensurate in scope with these claims. The specification fail to adequately enable one to find agents, other than anti-alpha/beta chain of MHC class I/II antibodies, which operably engage committed cells.

Claim 63 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a biological response modifier that is an alkylating agent, does not reasonably provide enablement for the use of any

biological response modifier of committed cells to become CD45 low expressing cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification fails to adequately enable one to find BRMs other than alkylating agents, which can be used in conjunction with anti-alpha/beta chain of MHC class I/II antibodies, to transform committed cells into CD45 low cells.

Applicant's response (page 10) to these scope of enablement rejections is that claims of like scope have been issued in Pat. 6,090,625. As noted supra regarding 112, first paragraph rejections, what was previously issued is not relevant to the present considerations.

The examiner, furthermore, maintains the enablement rejection on the basis that, while screening assays may have been disclosed to obtain the required agents or modifiers, undue trial and error would be involved since one still needs to obtain these products to practice what is claimed. See Univ. of Rochester v. G. D. Searle & Co. 68 USPQ 2d 1424 at page 1436-1438.

The 101/112 utility/how to use rejection of record is maintained infra.

Claims 47-76 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

As noted in the previous Office Actions applicant did not point out a specific or substantial utility for the CD45 low cells.

Claims 47-76 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant has urged that Wickenhauser et al teach that human hemopoietic stem cells that are CD34+ and CD45 low have a hemopoietic/myeloid potential. From the submitted/abstract, the examiner cannot find any teaching by Wickenhauser et al of CD45 low cells. They refer, rather, to a population in which "medullary CD34 progenitors expressed CD45." Wickenhauser et al thus do not show a utility for CD45 low cells obtained by the method of the claims.

Applicant has urged that several authors show CD45 low cells were useful in research. This argument is utterly unconvincing, since "research" does not constitute utility. Brenner V. Manson 148 USPQ 689. Further, from a review of the abstracts of the papers noted by applicant, the examiner finds that the authors are using the CD45 antigen as a marker (detected by antibodies thereto) to define various subsets of cells. In no case have these authors obtained an undifferentiated population of CD45 low cells, nor even have they detected such a population, and taught a utility for these cells, such as what they could be differentiated to become committed cells.

Applicant has urged that Zhao et al teach that the cells can be considered candidates for transplantation therapy. The examiner finds that the PSC cells taught by Zhao et al express the markers CD14, CD34 and CD45. These authors do not teach any use for a "CD45 low" population. (If the expression of CD45 noted by Zhao et al

would be what applicant considers as "CD45 low", then this is a further indication that the term "CD45 low" is indefinite and without an established meaning in the art).

Furthermore Zhao et al post-dates applicant's filing date; as such, this reference fails to show any established utility.

In essence applicant may have disclosed what to do with CD34+ stem cells; however, she has not disclosed what, in particular, one should do with the subpopulation thereof that is "CD45 low"; applicant has not disclosed what this subpopulation should be used for, that the more general CD34+ population would not be used for.

Claims 47-72 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,090,625. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims are claiming essentially the same process. See rational set forth in paper 8, at pages 10-11.

It is noted in applicant's response, that a terminal disclaimer will be filed, once claims are allowable on other grounds.

Applicant's urgings filed 5/13/03 have been considered but are unconvincing.

In addition to the above considerations, set forth in response to applicant's traversals of the rejections of record, the examiner herein below notes the following with respect to the 35 USC 112 first paragraph, lack of possession and scope of enablement rejections.

Regarding the agents that "operably engage" committed cells such that the relative number of CD45 low cells increases, the examiner properly considers that the applicant was not in possession of the genus of such agents because she misdescribed the functional nature of the agents. Likewise the examiner considers that the teachings of the specification fail to enable one to obtain any such agent, other than antibodies directed to the alpha or beta chain of MHC/HLA class I or class II receptors, because she misdirected the reader regarding the functional nature of the agents that one should screen for.

The examiner contends that the binding of the exemplified CR3/43 antibody to the hematopoietic cell containing sample induced selective apoptosis in the committed cells in the sample. The evidence for this phenomenon is set forth in

1. Pettersen et al, (Journal of Immunology, 1998, vol. 160, pp. 4343-4352), who teach that binding of monoclonal antibodies to HLA-A2 class I alpha-2 domain induces apoptotic cell death (abstract),
2. Genestier et al (Blood, 1997, vol.90, pp. 3626-3639) and Genestier et al (Blood, 1997, vol.90, pp. 726-735) who teach that two monoclonal antibodies which bind to an epitope of the alpha-1 domain induces apoptotic cell death of activated, but not resting peripheral T-lymphocytes (abstract), and B-cells (abstract), respectively.
3. Woodle et al, (Journal of Immunology, 1997, vol. 158, pp. 2156-2164) who teach that an antibody which recognizes the alpha-3 domain induces apoptosis in T-cells (abstract),

4. Vidovic and Toral (Cancer Letter, 1998, vol. 128, pp. 127-135) teach that incubation of monoclonal antibody which binds to HLA-DR of tumor B-cells induced apoptosis selectively in malignant B-cells (abstract, and page 130, second column, first and second full paragraphs).

5. Thibeault et al (Cellular Immunology, 1999, vol. 192, pp. 79-85) teach that binding of antibodies to HLA-DR on monocytes induces apoptotic monocyte death (abstract).

6. Berto et al (Journal of Immunology, 2000, vol. 164, pp. 2379-2385) teach that binding of monoclonal antibodies to HLA-DR of mature dendritic cells of monocytic origin led to marked apoptosis in said mature cells, but significantly less apoptosis was observed in immature dendritic cells (abstract, and page 2380, second column, under the heading "Detection of HLA-DR induced cell death").

7. the abstract of Tawara et al (Blood, 2001, vol. 98, pp. 250-B) which teaches that HLA-DR monoclonal antibodies induce apoptosis in B-cell lymphomas.

It appears that the preponderance of data supports the induction of apoptosis upon binding of antibodies to the HLA receptor. It is further concluded from the work of Berto et al that this induction of apoptosis is favored in more mature cells, which conclusion explains the observation set forth in the instant specification, that the phenotype of the samples had changed after addition of the CR3/43 monoclonal antibody. One of skill in the art would conclude that in light of the above publications, selective apoptosis was induced in the non-stem cell portion of the sample, and that repopulation of the sample took place in vitro by the stem cells remaining in the mixture.

The examiner considers that it is not necessary for applicant to have stated the true mechanistic basis for the changes observed in the exemplified cell culturing experiments. However, if a false mechanistic basis has been stated, such that it leads to an improper description of the functional nature and properties of the agents that one should use in the claimed method, and such that it provides improper direction as to how one would be enabled to screen for such agents, then applicant's claims must be limited to the use of those agents she has actually exemplified. Therefore, the further above rejections under 35 USC 112, first paragraph, pertaining to the lack description of the genus of agents and to the lack of scope enablement, are proper.

Copies of the references cited on form PTO-892 have not been provided. Each has been provided in an action of copending application 09/568,254.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Monday-Thursday from 8:00a.m to 5:30p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-1600.

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Saunders/tgd

April 6, 2004

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